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Research Article

The Effect of the Antioxidant Drug "U-74389g" on Uterus Congestion During Ischemia Reperfusion Injury in Rats

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Abstract

Objective: This experimental study examined the effect of the antioxidant drug "U-74389G", on rat model and particularly in an uterus Ischemia Reperfusion (IR) protocol. The probable beneficial effect of that molecule was studied pathologically using mean Uterus Congestion (UC) lesions.

Materials and methods: 40 rats of mean weight 231.875 g were used in the study. UC lesions were evaluated at 60 min of reperfusion (groups A and C) and at 120 min of reperfusion (groups B and D), A and B without but C and D with U-74389G administration.

Results: U-74389G administration significantly decreased the predicted UC scores by 0.31 [without lesions] [-0.47 - -0.16] (p=0.0004). Reperfusion time kept non-significantly increased the predicted UC scores by 0.10 [without lesions] [-0.21- 0.12] (p=0.2845). However, U-74389G administration and reperfusion time together produced a significant combined effect in decreasing the predicted UC scores by 0.17 [without lesions] [-0.27 - -0.08] (p=0.0005).

Conclusion: U-74389G administration whether it interacted or not with reperfusion time, significantly short-term kept the UC lesions scores unaltered.

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Introduction

Permanent or transient damage with serious implications on adjacent organs and certainly on patients' health may be due to tissue Ischemia and Reperfusion (IR). Although important progress has been made regarding the usage of U-74389G in managing this kind of damages, satisfactory answers have not been given yet to fundamental questions, as, by what velocity this factor acts, when should it be administered and at what dosage. The particularly satisfactory action of U-74389G as antioxidant agent has been noted in several performed experiments. However, just few relative reports were found concerning U-74389G trial in IR experiments, not covering completely this particular matter. Also, a lot of publications addressed trials of other similar antioxidant molecules to which the studied molecule also belongs to. U-74389G or better 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione maleate salt [1] is an antioxidant which prevents both arachidonic acid-induced and iron-dependent lipid peroxidation. It protects against IR injury in animal heart, liver and kidney models. These membrane-associating antioxidants [2] are mainly effective in preventing permeability changes in brain microvascular endothelial cells monolayers. A meta-analysis of 14 published seric variables, coming from the same experimental setting, tried to provide a numeric evaluation of U-74389G efficacy at the same endpoints (Table 1).

The aim of this experimental study was to examine the effect of U-74389G on rat model and particularly in an uterus IR protocol. The beneficial effect or non-effectiveness of that molecule was studied by evaluating Uterus Congestion (UC) lesions.

Materials and Methods

Animal preparation

This experimental study was licensed by veterinary address of East Attiki Prefecture under 3693/12-11-2010 & 14/10-1-2012 decisions. Everything needed for the study including consumables, equipment and substances were a courtesy of Experimental Research Centre of ELPEN Pharmaceuticals Co. Inc. SA at Pikermi, Attiki. Accepted standards of humane animal care were adopted for Albino female Wistar rats 16-18 weeks old. Normal housing in laboratory 7 days before the experiment included ad libitum diet. Post-experimental awakening and preservation of the rodents was not permitted even if euthanasia was needed. They were randomly delivered to four experimental groups by 10 animals in each one. Ischemia for 45 min followed by reperfusion for 60 min (group A). Ischemia for 45 min followed by reperfusion for 120 min (group B). Ischemia for 45 min followed by immediate U-74389G Intravenous (IV) administration and reperfusion for 60 min (group C). Ischemia for 45 min followed by immediate U-74389G IV administration and reperfusion for 120 min (group D). The molecule U-74389G dosage was 10 mg/Kg body weight of animals. U-74389G is liquid dissolved in water for injection. The control group was set indeed in equal amount of water for injection.

The detailed preceded prenarcotic and general anesthesiologic techniques are described in related reference [3]. Oxygen supply,

Variable	1h rep	p-value	1.5h rep	p-value	2h rep	p-value	interaction of U-74389G and rep	p-value
RBC	+1.39%±0.71%	0.7161	+0.64%±0.32%	0.8106	-0.10%±0.05%	0.9762	+1.05%±0.53%	0.4911
Hemoglobin	+5.2%±2.8%	0.0925	+3.9%±2.1%	0.0604	+2.7%±3.2%	0.3544	+2.5%±1.3%	0.0423
Mean corpuscular hemoglobin	+1.77%±0.96%	0.0663	+2.40%±0.57%	0.0001	+3.03%±0.71%	0.0003	1.33%±0.36%	0.0005
Platelet-crit	+3.80%±9.87%	0.6373	+9.23%±6.29%	0.1064	+14.66%±9.03%	0.0833	+6.72%±3.73%	0.0712
PDW	+1.1%±0.88%	0.2368	+1.79%±0.76%	0.0314	+2.49%±1.33%	0.0807	+0.96%±0.46%	0.0396
Glucose	-6.41%±3.50%	0.0663	-8.57%±2.06%	0.0001	-10.74%±2.52%	0.0003	-4.76%±1.28%	0.0005
Total protein	-5.48%±2.99%	0.0663	-7.34%±1.76%	0.0000	-9.20%±2.16%	0.0000	-4.08%±1.10%	0.0000
Alkaline phosphatase	+22.66%±12.37%	0.0663	+31.91%±7.69%	0.0001	+41.16%±9.65%	0.0003	+17.75%±4.79%	0.0005
Creatine phosphokinas	+54.32%±13.75%	0.0012	+35.34%±17.20%	0.0260	+16.37%±30.24%	0.495	+18.52%±9.44%	0.0770
Sodium	+1.22%±0.66%	0.0707	+0.17%±0.61%	0.7714	-0.87%±1.03%	0.3995	-0.32%±0.36%	0.3693
Chloride	-0.58%±0.77%	0.4533	-0.97%±0.53%	0.0879	-1.36%±0.76%	0.1113	-0.75%±0.38%	0.0159
Calcium	0%±1.75%	1	-0.14%±1.10%	0.8782	-0.28%±1.54%	0.8492	+0.14%±0.64%	0.8245
Phosphorus	-2.23%±5.51%	0.7966	-1.61%±3.32%	0.5789	-1%±4.48%	0.8129	-1.09%±2%	0.5771
Magnesium	+1.33%±3.59%	0.7033	-0.28%±2.75%	0.9171	-1.90%±5.28%	0.7161	+0.36%±4.58%	0.8228
Mean	+5.57%±15.58%	0.3552	+4.74%±12.98%	0.3049	+3.92%±12.98%	0.3485	+2.73%±7.06%	0.2380

Table 1: The U-74389G influence (±SD) on the levels of some seric variables3 concerning reperfusion (rep) time.

electrocardiogram and acidometry were continuously provided during whole experiment performance.

The protocol of IR was followed. Ischemia was caused by laparotomic forceps clamping inferior aorta over renal arteries for 45 min. Reperfusion was induced by removing the clamp and reestablishment of inferior aorta patency. The molecules were administered at the time of reperfusion, through catheterized inferior vena cava. The UC lesions evaluations were performed at 60 min of reperfusion (for groups A and C) and at 120 min of reperfusion (for groups B and D). Forty (40) female Wistar albino rats were used of mean weight 231.875 g [Std. Dev: 36.59 g], with min weight ≥ 165 g and max weight ≤ 320 g. Rats' weight could be potentially a confusing factor, e.g., the more obese rats to have higher UC scores. This suspicion was investigated. Also, detailed pathological study [4] and grading of UC findings was performed by scores, this is: 0 lesions were not found, 1 mild lesion was found, 2 moderate lesions were found and 3 serious lesions were found. The previous grading is transformed as follows: (0-0.499) without lesions, (0.5-1.499) mild lesions, (1.5-2.499) moderate lesions and (2.5-3) serious lesions damage, because the study concerns score ranges rather than point scores.

Model of ischemia reperfusion injury

Control groups: 20 control rats of mean weight 252.5 g [Std. Dev: 39.31 g] experienced ischemia for 45 min followed by reperfusion.

Group A: Reperfusion which lasted 60 min concerned 10 control rats of mean weight 243 g [Std. Dev: 45.77 g] and mean moderate mild UC score 1.4 [Std. Dev: 0.51] (Table 2).

Group B: Reperfusion which lasted 120 min concerned 10 control rats of mean weight 262 g [Std. Dev: 31.10 g] and mean mild UC score 1.1 [Std. Dev: 0.31] (Table 2).

Lazaroid (L) group: 20 rats of mean weight 211.25 g [Std. Dev: 17.53 g] experienced ischemia for 45 min followed by reperfusion in the beginning of which 10 mg U-74389G /kg body weight were IV administered.

Group C: Reperfusion which lasted 60 min concerned 10 L rats of mean weight 212.5 g [Std. Dev: 17.83 g] and mean without lesions UC score 0.3 [Std. Dev: 0.48] (Table 2).

Group D: Reperfusion which lasted 120 min concerned 10 L rats of mean weight 210 g [Std. Dev: 18.10 g] and mean without lesions UC score 0.4 [Std. Dev: 0.5163978] (Table 2).

Groups	Variable	Mean	Std. Dev
A	Weight	243 g	45.77 g
	UC	mild 1.4	0.51
B	Weight	262 g	31.10 g
	UC	mild 1.1	0.31
C	Weight	212.5 g	17.83 g
	UC	without lesions 0.3	0.48
D	Weight	210 g	18.10 g
	UC	without lesions 0.4	0.51

Table 2: Weight and Uterus Congestion (UC) score mean levels and Std. Dev. of groups.

Statistical analysis

Everyone from 4 rat's weight groups was compared with each other and from 3 remained groups applying statistical paired t-test (Table 3). Any emerging significant difference among UC scores was investigated whether it was owed in the above mentioned significant weight correlations. Also, everyone from 4 rats UC scores groups was compared with each other from 3 remained groups applying Wilcoxon signed-rank test (Table 3). The application of Generalized Linear Models (GLM) with dependant variable the UC scores and independent variables the U-74389G administration or no, the reperfusion time and their interaction was followed. Inserting the rats weight also as an independent variable at GLM analysis, a significant relation results in (p=0.0047), so as to further investigation was needed. The predicted UC scores adjusted for rat's weight were calculated and are depicted at table 4. The differences between predicted mean UC scores as calculated by Wilcoxon signed-rank tests are depicted at table 5. The application of GLM with dependant variable the predicted UC scores and independent variables the U-74389G administration or no, the reperfusion time and their interaction was followed.

DG	Variable	Difference	p-value
A-B	Weight	-19 g	0.2423
	UC	without lesions 0.3	0.0833
A-C	Weight	30.5 g	0.0674
	UC	mild 1.1	0.0067
A-D	Weight	33 g	0.0574
	UC	mild 1	0.0102
B-C	Weight	49.5 g	0.0019
	UC	mild 0.8	0.0092
B-D	Weight	52 g	0.0004
	UC	mild 0.7	0.0154
C-D	Weight	2.5 g	0.7043
	UC	without lesions -0.1	0.5637

Table 3: Statistical significance of mean values Difference for Groups (DG) after statistical paired t test application for weight and Wilcoxon signed-rank test for scores.

Groups	Mean	Std. Dev
A	mild 0.88	0.51
B	mild 1.03	0.31
C	mild 0.64	0.48
D	mild 0.63	0.51

Table 4: Weight and predicted UC score mean levels and Std. Dev. of groups.

DG	Difference	p-value
A-B	without lesions -0.14	0.1843
A-C	without lesions 0.23	0.0745
A-D	without lesions 0.25	0.0743
B-C	without lesions 0.38	0.0093
B-D	without lesions 0.40	0.0069
C-D	without lesions 0.01	0.9182

Table 5: Statistical significance of mean values Difference for Groups (DG) after Wilcoxon signed-rank test application for predicted UC scores.

Results

The first GLM application resulted in: U-74389G administration significantly decreased the UC scores by 0.9 [mild lesions] [-1.19 - -0.60] (p=0.0000). This finding was in accordance with the results of Wilcoxon signed-rank test (p=0.0003). Reperfusion time non-significantly decreased the UC scores by 0.1 [without lesions] [-0.51 - 0.31] (p=0.6320), approximately in accordance with the Wilcoxon signed-rank test result altered by 0 [without lesions] [-0.33 - 0.33] (p=1.0000). However, U-74389G administration and reperfusion time together produced a significant combined effect in decreasing the UC scores by 0.47 [without lesions] [-0.67 - -0.27] (p=0.0000). Reviewing the above and table 3, table 6 sums up concerning the decreasing influence of U-74389G in connection with reperfusion time. The second GLM application resulted in: U-74389G administration significantly decreased the predicted UC scores by 0.31 [without lesions] [-0.47 - -0.16] (p=0.0001). This finding was in accordance with the results of Wilcoxon signed-rank test (p=0.0008). Reperfusion time non-significantly increased the predicted UC scores by 0.06 [without lesions] [-0.11 - 0.24] (p=0.4831), approximately in accordance with the Wilcoxon signed-rank test result increased by 0.14 [without lesions] [-0.30 - 0.00] (p=0.0859). However, U-74389G administration and reperfusion time together produced a significant combined effect in decreasing the predicted UC scores by 0.17 [without lesions] [-0.27 - -0.08] (p=0.0005). Reviewing the above and table 5, the table 7 and 8 sum up concerning the decreasing influence of U-74389G in connection with reperfusion time. Figure 1, depicts uterus congestion due to uterus layers becoming swollen from inflamed blood vessels, just before reperfusion. The increase of blood in uterus layers seems in this figure 1, due to dilatation of small vessels. Active congestion is a result of arteriolar distension due to inflammation and local neuro-vegetative reaction and passive congestion also termed stasis, as a consequence of an impaired venous drainage (compression or obstruction of veins), followed by dilatation of venules and capillaries. Central veins and central vascular sinusoids are dilated, compressing the endometrial and myometrial cells which are atrophied and with progression, will necrotize - central hemorrhagic necrosis (compression and/or ischemic mechanism). Median cells may present fatty change (hypoxic mechanism).

Decrease	95% c. in	Reperfusion time	Wilcoxon	p-values glm
mild 1.1	-1.56 - -0.63	1h	0.0067	0.0001
mild 0.9	-1.19 - -0.60	1.5h	0.0003	0.0000
mild 0.7	-1.10 - -0.29	2h	0.0154	0.0018
without lesions 0.1	-0.51 - 0.31	reperfusion time		0.632
without lesions 0	-0.33 - 0.33	reperfusion time	1.0000	
without lesions 0.47	-0.67 - -0.27	Interaction		0.0000

Table 6: The decreasing influence of U-74389G in connection with reperfusion time.

Decrease	95% c. in	Reperfusion time	Wilcoxon	p-values glm
without lesions 0.23	-0.48 - 0.01	1h	0.0745	0.0653
without lesions 0.31	-0.47 - -0.16	1.5h	0.0008	0.0001
without lesions 0.40	-0.58 - -0.21	2h	0.0069	0.0002
without lesions -0.06	-0.11 - 0.24	reperfusion time		0.4831
without lesions -0.14	-0.30 - 0.00	reperfusion time	0.0859	
without lesions 0.17	-0.27 - -0.08	interaction		0.0005

Table 7: The predicted decreasing influence of U-74389G in connection with reperfusion time.

Decrease	95% c. in	Reperfusion time	p-values
without lesions 0.23	-0.48 - 0.01	1h	0.0699
without lesions 0.31	-0.47 - -0.16	1.5h	0.0004
without lesions 0.40	-0.58 - -0.21	2h	0.0035
without lesions -0.10	-0.21- 0.12	reperfusion time	0.2845
without lesions 0.17	-0.27 - -0.08	interaction	0.0005

Table 8: Concise presence of the decreasing influence of U-74389G in connection with reperfusion time.

Discussion

Uterine congestion happens [5], when the uterus becomes swollen by excess fluid due to membranes lining swelling from inflamed blood vessels. The increased peripheral resistance and greater blood volume place further strain on the uterus and accelerates the process of damage to the myometrium. Vasoconstriction and fluid retention produce an increased hydrostatic pressure in the capillaries. This shifts the balance of forces in favor of interstitial fluid formation as the increased pressure forces additional fluid out of the blood, into the tissue. This results in edema (fluid build-up) in the tissues. This

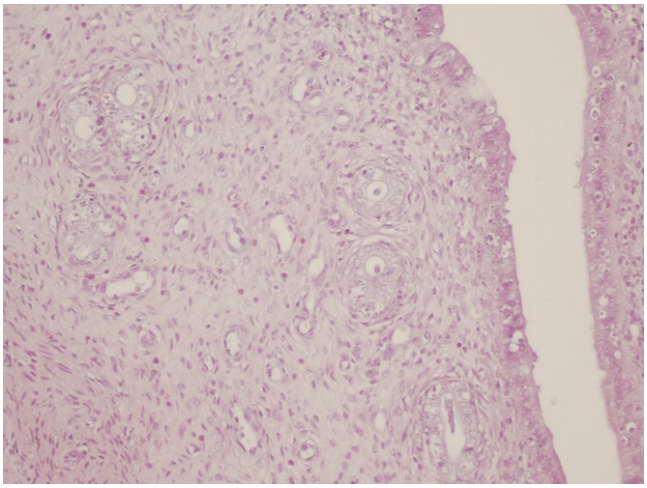

Figure 1: Depicts uterus congestion with its swollen layers, distended arteries, dilated small vessels, capillaries, venules, central veins, compressed and atrophied endometrial and myometrial cells either with central hemorrhagic necrosis or the median ones fatty changed.

causes stiffening of the uterus and reduces the efficiency of gas exchange by increasing the distance between the air and the blood. Increased volume or pressure in the uterine veins impairs the normal drainage of the uterus and favors the flow of fluid from the capillaries to the myometrium parenchyma, causing endometrial edema. This impairs endometrial oxygenation.

The following situations show the association between ischemia and congestion in uterus. Salas SP postulated [6] that cerebral congestion, secondary to compression of the abdominal organs by the large uterus, diverts blood to the brain, causing eclamptic convulsions. Surcel VJ et al., showed that uterus fibroma has always been accompanied by pelvic congestion inducing [7] experimentally estrogen tumors in animals. Douglas BH observed liver and renal glomerular congestion both in pregnant and non-pregnant rats producing [8] hypertension, however, only in pregnant ones.

Lazaroids, a novel series of glucocorticoid compounds 21-aminosteroids have the properties of free radical scavenging. U-74389G is one of the 132 similar lazaroid compounds. It has a molecular weight of 726.90406 g/mol; it has a selective action on vascular endothelium with vitamin E-like properties. The most famous activity is that of neuroprotective and membrane-stabilizing properties. Although it accumulates in the cell membrane, thus protecting vascular endothelium from peroxidative damage hardly penetrates the blood-brain barrier. More specifically, Hori H et al., showed [9] its excellent effect on central nervous system trauma and ischemia. The degree of elevation of action potential thresholds and the rate of missing outer hair cells were significantly reduced demonstrating that U-74389G has a protective effect on cisplatin-induced ototoxicity without glucocorticoid action. Schmid-Elsaesser R et al., showed [10] significantly less neurologic deficits postoperatively and significantly reduced cortical infarct volumes by the neuroprotective microvascularly acting 21-aminosteroid U-74389G. Passaquin AC et al., elicited [11] a beneficial effect of glucocorticoids in Duchenne muscular dystrophy, attributing it to a reduction of the pathological increase in Ca^{++} influx via an effect on the sarcolemma of C2C12 skeletal muscle cells. van Klaveren RJ et al., supposed that direct inactivation of the membrane-bound γGT by hyperoxia is the most likely mechanism for the increased [12] γGT, SOD, and GSH levels in oxygen-exposed cells by U-74389G. Schmid-Elsaesser R et al., concluded [13] that antioxidative compounds which cross the blood-brain barrier are more effective in focal cerebral ischemia than agents which predominantly act on the endothelium of cerebral microvessels. Lehmann C et al., decreased [14] TNF_{α} release during endotoxemia permitting treatment of septic states. As immunosuppressant it may act through activation of T-cells or by inhibiting the activation of helper cells. While immunosuppression primarily prevents rejection of transplanted organs, new applications involving mediation of the effects of interleukins and other cytokines are emerging. Lehmann C et al., attenuated [15] leukocyte adherence and their rolling behavior in intestinal venules which is found increased during endotoxemia. Horáková L et al., [16] calculated the preventive effect concerning lipid peroxidation at 160 IC50 μmol/l by U 74389G in oxidative stress. Heim C et al., totally prevented [17] the learning impairments, suggesting that lipid peroxidation may be responsible for the late learning deficiencies. Vlkolinský R revealed [18] protective activity on Synaptic Transmission (ST) recovery and on $t_{1/2}$ during hypoxia; a protective potency of U-74389G on Population Spikes (PoS) recovery and a possibility to delay the early ST decay during hypoxia, which might indicate improved energetic state of neurons in the treated tissue. Durmaz R et al., [19] showed antiproliferative properties on cancer cells calculating an IC50 value at 91 m mM. Kondziolka D et al., prevented [20] regional edema favoring radiosurgery, surrounding brain protection without reducing the desired therapeutic effect.

Uterine congestion can be met at many clinical situations. Smith CC et al., assessed [21] intravascular growth in 20% of 41 leiomyoma patients median aged 46 years old but this finding is apparently devoid of clinical significance due to limited data. Typical presence included menorrhagia; average tumor size 15.4 cm; most exophytic, usually contiguous with the intramural dissecting leiomyomatous components but typically isointense to myometrium, multinodular, occasionally cystic masses with a congested, spleen or placenta-like color, protruding over the uterine serosa and variably, the broad ligaments and adjacent organs. Hu LQ et al., displayed [22] loosened cervical tissue with significantly lessened, swollen, convoluted and ruptured collagen fiber, showing sparse disorderly lined-up reticular status in rats after pitocin medication. Degradation of collagen fiber, vascular dilatation and congestion with massive amount of inflammatory cells infiltration, increased matrix components, many leucocytes, fibroblast in the stroma and higher cervical score were also displayed in treated group than placebo ($P<0.05$). Gaspard UJ et al., noted [23] in decreasing order of frequency mastalgia, vaginal discharge, nausea, abdominal and leg cramps, headaches, weight increase, spotting, breakthrough and withdrawal bleeding. 20% of women dropped out of the study essentially for breast tenderness, weight increase, spotting and nausea during continued 10 cycles use of a new triphasic oral contraceptive (WL-49(50) 'Trinordiol') containing the lowest quantity of steroids in 75 healthy teenager young women. Singh ND et al., recorded [24] vascular changes and hemosiderosis in uterus associated with lymphocytic depletion and apoptosis in the lymphoid organs in induced toxic Wistar rats.

Conclusion

U-74389G administration whether it interacted or not with reperfusion time, significantly short-term keeps the UC lesions scores unaltered. Perhaps, a longer study time or a higher drug dose may reveal significant alteration.

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